NOVARTIS PATENT DEPT. CH

- 23 -

## What is claimed is:

1. A combination which comprises (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

- 2. A combination which comprises
  - (a) a HER-1 or a HER-2 antibody and
  - (b) an epothilone derivative of formula I

- 24 -

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl and Z is O,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

3. A combination which comprises (a) at least one antineoplastic agent selected from the group consisting of topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (b) an epothilone derivative of formula I

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O,

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

4. A combination which comprises (a) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors and antiestrogens and (b) an epothilone derivative of formula I - 25 -

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O.

in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.

- 5. Combination according to claim 1 which comprises (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I wherein A represents O or NR<sub>N</sub>, wherein R<sub>N</sub> is hydrogen or lower alkyl, R' is methyl or methylthio, R is hydrogen or lower alkyl, and Z is O, in which the active ingredients (a) and (b) are present in each case in free form or in the form of a pharmaceutically acceptable salt and optionally at least one pharmaceutically acceptable carrier; for simultaneous, separate or sequential use.
- Combination according to claim 1,2 or 5 wherein the HER-1 or HER-2 antibody is trastuzumab.
- 7. Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a topologmerase I inhibitor.
- 8. Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a topoisomerase II inhibitor.

- 26 -

- Combination according to claim 1, 4 or 5 wherein the antineoplastic agent is an aromatase inhibitor.
- 10. Combination according to claim 1, 3 or 5 wherein the antineoplastic agent is a microtubule active agent.
- 11. Combination according to claim 1 to 10 wherein the epothilone derivative is epothilone B.
- 12. Combination according to any one of claims 1 to 11 which is a combined preparation
- 13. Method of treating a warm-blooded animal having a proliferative disease comprising administering to the animal a combination according to any one of claims 1 to 9 in a quantity which is jointly therapeutically effective against a proliferative disease and in which the compounds can also be present in the form of their pharmaceutically acceptable salts.
- 14. A pharmaceutical composition comprising a quantity which is jointly therapeutically effective against a proliferative disease of a combination according to any one of claims 1 to 12 and at least one pharmaceutically acceptable carrier.
- 15. A combination according to any one of claims 1 to 12 for use in the treatment of a proliferative disease.
- 16. Use of a combination according to any one of claims 1 to 12 for the preparation of a medicament for the treatment of a proliferative disease.
- 17. Use according to claim 15 or 16 wherein the proliferative disease is a solid tumor disease.
- 18. Use of (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone

- 27 -

deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors in combination with (c) an epothilone derivative of formula I

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O,

for the preparation of a medicament for the treatment of a proliferative disease.

19. A commercial package comprising (a) a HER-1 or a HER-2 antibody or (b) at least one antineoplastic agent selected from the group consisting of aromatase inhibitors antiestrogens, topoisomerase I inhibitors, topoisomerase II inhibitors, microtubule active agents, protein kinase C inhibitors, anti-angiogenic compounds, gonadorelin agonists, anti-androgens, histone deacetylase inhibitors, and S-adenosylmethionine decarboxylase inhibitors and (c) an epothilone derivative of formula I

wherein A represents O or  $NR_N$ , wherein  $R_N$  is hydrogen or lower alkyl, R is hydrogen or lower alkyl, R' is methyl, methoxy, ethoxy, amino, methylamino, dimethylamino, aminomethyl or methylthio, and Z is O,

- 28 -

together with instructions for simultaneous, separate or sequential use thereof in the treatment of a proliferative disease.